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EDITORIAL

Insulin receptors and insulin actions in the nervous system

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Summary

Insulin receptors are widely distributed in the brain. They are also present in peripheral nerve. Insulin signaling through its receptors in the brain is responsible for the hormone's effects on the regulation of food intake, body weight, and reproduction. Signaling through the insulin receptor also appears to influence higher cognitive functions. In peripheral nerve, insulin signaling may play a role in the maintenance and repair of myelinated fibers. Future studies should determine the extent to which a defective insulin signal may be linked to the pathogenesis of diabetic neuropathies and neurodegenerative disorders such as Alzheimer's disease. Copyright © 2000 John Wiley & Sons, Ltd.

Keywords insulin receptors; insulin actions; central nervous system; peripheral nerve; diabetic neuropathy; Alzheimer's disease

The central nervous system

In 1978, Havrankova, Roth and Brownstein [1] demonstrated for the first time the presence of insulin receptors in the central nervous system (CNS), classically an 'insulin-insensitive' tissue. Since this seminal paper, numerous studies have been devoted to insulin receptors and insulin actions in the CNS. Insulin receptors are widely distributed in the brain, with much higher concentrations in neurons than in glia [for a review see 2]. They are found in both cell bodies and synapses. Distinct regional patterns of expression of the insulin receptor may reflect different functions.

One domain of insulin action in the CNS is related to the control of food intake through insulin receptors abundantly located in the olfactory bulb and thalamic nuclei. In fact, insulin was the first hormonal signal to be implicated in the control of body weight by the CNS [3]. Both insulin and leptin act as dual adiposity signals to the brain for the regulation of food intake and body weight [4]. Reduced CNS insulin delivery may be a feature of several different forms of obesity [5]. Like leptin, insulin signaling in the CNS plays a central role not only in participating in the regulation of food intake and body weight, but also in the regulation of reproductive function, as demonstrated very recently by Brüning *et al.* These researchers discovered that in addition to diet-sensitive obesity, mice with a neuron-specific disruption of the insulin receptor gene exhibit reduced fertility due to hypothalamic dysregulation of luteinizing hormone [6].

Another domain of insulin action in the CNS concerns cognitive functions. High levels of insulin receptors are present in the limbic system, particularly the hippocampus which is critically involved in spatial memory processing. Signaling through the insulin receptor appears to participate in this memory processing [7]. Acute intranasal administration of insulin has been shown to directly affect brain function [8]. In addition, defects in insulin action in the

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CNS may be linked to the pathogenesis of neurodegenerative disorders such as Alzheimer's [9] and Parkinson's [10] disease. In a review article published in the preceding issue of *Diabetes/Metabolism Research and Reviews*, Ryan and Geckle discussed the roles of ageing, Type 2 diabetes and insulin in learning and memory dysfunction [11].

And the peripheral nervous system?

In 1987, Waldbillig and LeRoith [12] showed that peripheral sensory and autonomic ganglia contain insulin receptors. In the preceding issue of *Diabetes/Metabolism Research and Reviews*, Sugimoto *et al.* [13] demonstrated the presence of insulin receptors in the sciatic nerve and dorsal root ganglion. Using both light and ultrastructural immunochemistry, these researchers further localized insulin receptors to the nodal and paranodal axolemma and Schwann cell plasma membranes. These sites of myelinated fibers are known to possess specialized molecular structures such as ion channels, Na^+/K^+-ATPase, glucose transporters, aldose reductase, and specialized molecules such as paranodin and integrins. Thus, in peripheral nerve the insulin receptor co-localizes with membrane molecules believed to play important roles in the maintenance of nodal function and structure, fiber regeneration and repair of myelinated fibers. It is tempting to speculate that signaling through the insulin receptor is involved in these functions, as suggested by the neurotrophic properties of insulin and insulin-like growth factors.

What are the pathophysiological implications?

As pointed out by Sugimoto *et al.* [13], one of the key differences between the neuropathy in the two types of diabetes is the progressive disruption of the paranodal ion-channel barrier in Type 1 diabetes. This alteration has been associated with the more severe conduction defect in Type 1 compared to Type 2 diabetes. Decreased insulin signaling due to insulinopenia may play a role in the functional and structural abnormalities of the nodal and paranodal apparatus in Type 1 diabetes. Also, the co-localization of the insulin receptors and integrins in the Schwann cell suggests that a decreased insulin signal may impair functions of the integrins and contribute to Schwann cell/myelin alterations in diabetic neuropathy.

Two other findings in the article of Sugimoto *et al.* [13] are of particular interest. In endoneurial microvessels, immunoelectron microscopy showed insulin receptor localization on plasma membranes of endothelial cells and pericytes/vascular smooth muscle cells; and high intensity of immunostained insulin receptor was found in close proximity to interendothelial tight junctions. These findings are consistent with the localization of insulin receptor in brain capillaries where insulin crosses the blood–brain barrier via receptor-mediated transcytosis. Sugimoto *et al.* also suggest an additional pathway for insulin passage at the interendothelial tight junction, and the possibility that insulin signaling is involved in the integrity of the blood–nerve barrier.

Nothing is presently known about the regulation of the insulin receptor and insulin signaling in peripheral nerve. Previous studies [for a review see 2] have suggested that, unlike peripheral (i.e. adipocyte, liver and muscle) insulin receptors, the brain insulin receptors do not undergo downregulation after exposure to high concentrations of insulin. If this is also true for peripheral nerve, then one may anticipate that alterations in insulin receptor (and insulin receptor signaling) would not occur in peripheral nerve as a result of hyperinsulinemia *per se*. Downregulation of insulin receptors, however, may still occur at the level of the blood–nerve barrier, allowing lesser amounts of insulin to be delivered into the nerve. Some degree of insulin deficiency may therefore affect the peripheral nerve even in hyperinsulinemic situations.

Exactly how insulin action in the brain can influence higher cognitive functions such as learning and memory is not yet fully understood. In patients with Alzheimer's disease, insulin has been reported to be higher in plasma and lower in cerebrospinal fluid when compared to control subjects [14]. One possible explanation for this discrepancy may be a lower rate of CNS insulin delivery as a result of insulin receptor downregulation at the level of the blood–brain barrier, as discussed above. In addition to diminished insulin signal, insulin action may also be impaired as a result of reduced insulin receptor tyrosine kinase activity in the Alzheimer's disease brain [9]. Also, in cultured human neurons, insulin and IGF-1 have been shown to reduce the phosphorylation of tau [15], a neuronal microtubule-associated protein that, in its hyperphosphorylated form, is the major component of the neurofibrillary lesions in Alzheimer's disease.

Conclusion

Clearly, the nervous system, both central and peripheral, is an important target of insulin action in health and disease. Many studies make a strong case for direct effects of insulin on the nervous system through its signaling network. Delineating the extent to which impaired insulin signaling is directly implicated in the pathogenesis of diabetic neuropathies and of neurodegenerative disorders such as Alzheimer's disease, and elucidating the mechanisms involved, represent new and exciting avenues of investigation, and potential promises for future development of novel therapeutic approaches.

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Oxidative stress in Parkinson's disease and other neurodegenerative disorders.

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The cause of cell death in neurodegenerative diseases remains unknown but the formation of free radicals and the occurrence of oxidative stress may be a common component of many, if not all, such disorders. For example, in substantia nigra in Parkinson's diseases key alterations occur, in iron handling, mitochondrial function and antioxidant defences, particularly reduced glutathione. These indices of oxidative stress are accompanied by evidence of free radical mediated damage in the form of increased lipid peroxidation and oxidation of DNA bases. The alterations in oxidative stress occurring in Parkinson's disease appear not be related to the administration of L-DOPA. Some alterations of oxidative stress are found in other basal ganglia in degenerative disorders (multiple system atrophy, progressive supranuclear palsy, Huntington's disease) but these have not been investigated to the same extent. Similarly, examination of biochemical changes occurring in Alzheimer's disease, motor neurone disease and diabetic neuropathy also suggest the involvement of free radical mediated mechanisms as a component of neurodegeneration. It is probable that irrespective of the primary cause of individual neurodegenerative disorder, the onset of oxidative stress is a common mechanism by which neuronal death occurs and which contributes to disease progression. Clearly, therapeutic strategies aimed at limiting free radical production and oxidative stress and/or damage may slow the advance of neurodegenerative disease.

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